

GUIDE TO CHRONIC PAIN ASSESSMENT & MANAGEMENT IN PRIMARY CARE

DEFINITION OF CHRONIC PAIN

Chronic non-cancer pain is the persistence of disabling symptoms of pain lasting greater than 3 months in duration, despite adequate medical intervention.

KEY MESSAGES FOR THE PATIENT

- ☞ "I understand that you are in pain. It's not all in your head—it is a real medical condition."
- ☞ "Your active role in the management of your chronic pain will help improve your quality of life."
- ☞ "Let's talk about setting realistic treatment goals. We can aim to decrease your pain and suffering to improve your day-to-day functioning."
- ☞ "You will have better and worse days in your daily activities, but there are things you can do to feel better."
- ☞ "Some people worry about their pain treatment and medications. Tell me your concerns."
- ☞ "Often, we involve behavioral medicine or a behavioral medicine specialist because we recognize chronic pain affects so many aspects of your life. It does not mean that your pain is not real or that you have a psychiatric problem."

KEY PRINCIPLES OF CHRONIC PAIN MANAGEMENT

- **PROMOTE GOOD COMMUNICATION BETWEEN YOURSELF & YOUR PATIENT**
Validate your patient's pain, set realistic treatment goals, and help address major barriers to pain management. Support good communication using the "Key Messages for the Patient."
- **SUPPORT THE ACTIVE ROLE OF THE PATIENT**
Self-care is an integral part of the successful management of chronic pain. Your patient should be encouraged and supported to actively engage in self-management therapies to improve symptom management, promote independent functioning, and enhance psychosocial well-being.
- **OPTIMIZE MEDICATION USE**
Appropriate medication management, especially in opioid analgesic therapy, is essential for relieving suffering and returning a chronic pain patient to function.
- **UTILIZE A MULTIDISCIPLINARY, MULTIMODAL APPROACH**
 - A *multidisciplinary approach* involves a wide range of clinicians—e.g., physical therapist, health psychologist, addiction medicine specialist, primary care physician—with multiple skills—e.g., rheumatology, neurology—interacting as a team for the coordinated care management of the chronic pain patient.
 - *Multimodal treatment* is defined as concomitant use of separate therapeutic interventions—e.g., medication, cognitive behavioral therapy, interventional procedures—to obtain additive beneficial effects or reduction of adverse effects.

SCREENING

ASK YOUR PATIENT, "DO YOU HAVE PAIN OR DISCOMFORT NOW?" in the following situations:

- When patients present with musculoskeletal or neuropathic conditions
- After any known pain-producing procedure
- When there is a high probability of pain associated with patient's reason for visit or with their medical history

If pain is acute (<3 months), consider the following risk factors for developing chronic pain:

- In patients with acute herpes zoster pain
 - Unrelieved severe pain intensity
 - Advanced age (>60 years old)
- In patients with acute low back pain
 - Previous history of low back pain
 - Unrelieved severe pain intensity
 - Poor functional status (or level of disability)
 - Low level education
 - Self-perceived risk of developing a chronic problem
 - Psychosocial factors: psychological distress, stressful life events, depression
- In patients with acute neck pain
 - Self-perceived risk of developing a chronic problem
- In patients with acute musculoskeletal pain
 - Lack of active coping skills, e.g., realistic goal setting, pacing, realistic beliefs about condition

Being involved in litigation related to an accident that caused pain may be associated with a progression to chronicity, although there is limited evidence from the primary care setting.

If pain is chronic (≥ 3 months), assess the severity and pain-related disability outlined on page 2.

ASSESSMENT

RATE THE PAIN. Ask your patient to rate the severity of pain from 0 ('no pain')–10 ('worst pain imaginable'). This is called the Numerical Rating Scale (NRS).

ASK GENERAL QUESTIONS ABOUT THE PAIN. If reported pain is between 1–6 on the NRS (mild to moderate pain), typical characteristics of pain sought during the history taking process include:

- Pain onset
- Pain quality
- Pain duration
- Pain variability
- Pain severity (*see tool below*)
- Pain-related disability (*see tool below*)
- Interference with activities of daily living (e.g., eating, bathing, dressing) (*see tool below*)
- Previous pain experiences and treatments
- Treatment goal

FOR SEVERE PAIN, ASK ADDITIONAL QUESTIONS. If reported pain is between 7–10 on the NRS (severe pain), or pain continues despite routine care, further investigation is warranted.

- Consider the following—alleviating and aggravating patterns, quality of life indicators (interference of pain in sleep, relations with other

people), and life stressors. A pertinent physical examination should be completed.

- Other considerations that may require more comprehensive assessment and may indicate a more refractory course include the presence of:
 - Red flags which increase the probability of more serious underlying conditions—cancer, infection, cauda equina syndrome, and fracture (*see page 6 for an example of red flags*)
 - Depression* and anxiety
 - Domestic violence or sexual abuse
 - Substance abuse
 - Cognitive impairment

WHEN TO REFER TO PAIN MEDICINE SPECIALISTS. In the absence of any serious underlying condition and/or if pain continues to be poorly controlled despite aggressive attempts at management by the primary care physician, referral to one or more pain medicine specialists to conduct a comprehensive assessment may be warranted.

Cultural and gender norms and values regarding pain and the expression of pain can vary. Utilize cross-culturally validated tools (e.g., Brief Pain Inventory available in the CMI Chronic Pain Management Program), certified medical interpreters, or translated assessment tools when necessary to ensure accurate assessment of pain for all patients.

*The prevalence of Major Depression in chronic pain patients ranges from 5%–72%.



Tool: Chronic Pain Grade Questionnaire (CPG)

This self-assessment instrument can be administered by the clinician or other clinic staff. Copies of this tool and a pain map can be found in the CMI Chronic Pain Management Program.

1. In the past week, on the average, how intense was your pain rated on a 0 to 10 scale where 0 is "no pain" and 10 is "pain as bad as could be"? (That is, your usual pain at times you were experiencing pain)

NO PAIN												PAIN AS BAD AS COULD BE
0	1	2	3	4	5	6	7	8	9	10		

2. About how many days in the past week have you been kept from your usual activities (work, school, or housework) because of (anatomical site) pain?

Disability Days

3. In the past week, how much has (anatomical site) pain interfered with your daily activities rated on a 0 to 10 scale where 0 is "no interference" and 10 is "unable to carry on any activities"?

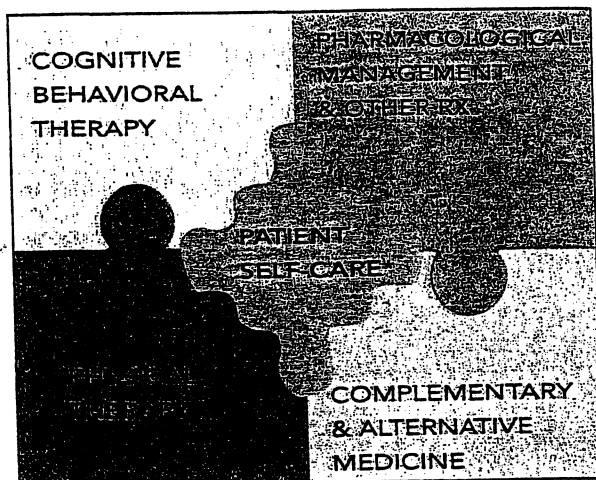
NO INTERFERENCE												UNABLE TO CARRY-ON ANY ACTIVITIES
0	1	2	3	4	5	6	7	8	9	10		

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TREATMENT

The following modalities should be considered as part of a coordinated, multimodal, multidisciplinary treatment plan. Self-care plays a central role in the success of any treatment plan.

Although there is no single sequence for using pharmacological and non-pharmacological interventions in combination, we do recommend a sequence for pharmacological management on page 4.



* See Key Messages on page 1 and refer to patient educational resources in the CMI Chronic Pain Management Program.

CULTURAL CONSIDERATIONS

Gender and ethnicity affect the experience, expression, and adjustment to chronic pain. Females are at greater risk than males for developing several chronic pain disorders and various ethnic groups report worse or better adjustment to chronic pain than white patients. This has major implications for the identification and assessment of pain and potential undertreatment of chronic pain. Clinicians need to be aware of cultural health care beliefs and expectations of patients for effective patient-clinician communication and understanding as well as creating mutually acceptable treatment plans.

The following link is to the CMI Culturally Competent Care Pocket Card created by CMI and the Institute for Culturally Competent Care and provider handbooks for the major ethno-cultural groups comprising Kaiser Permanente membership.

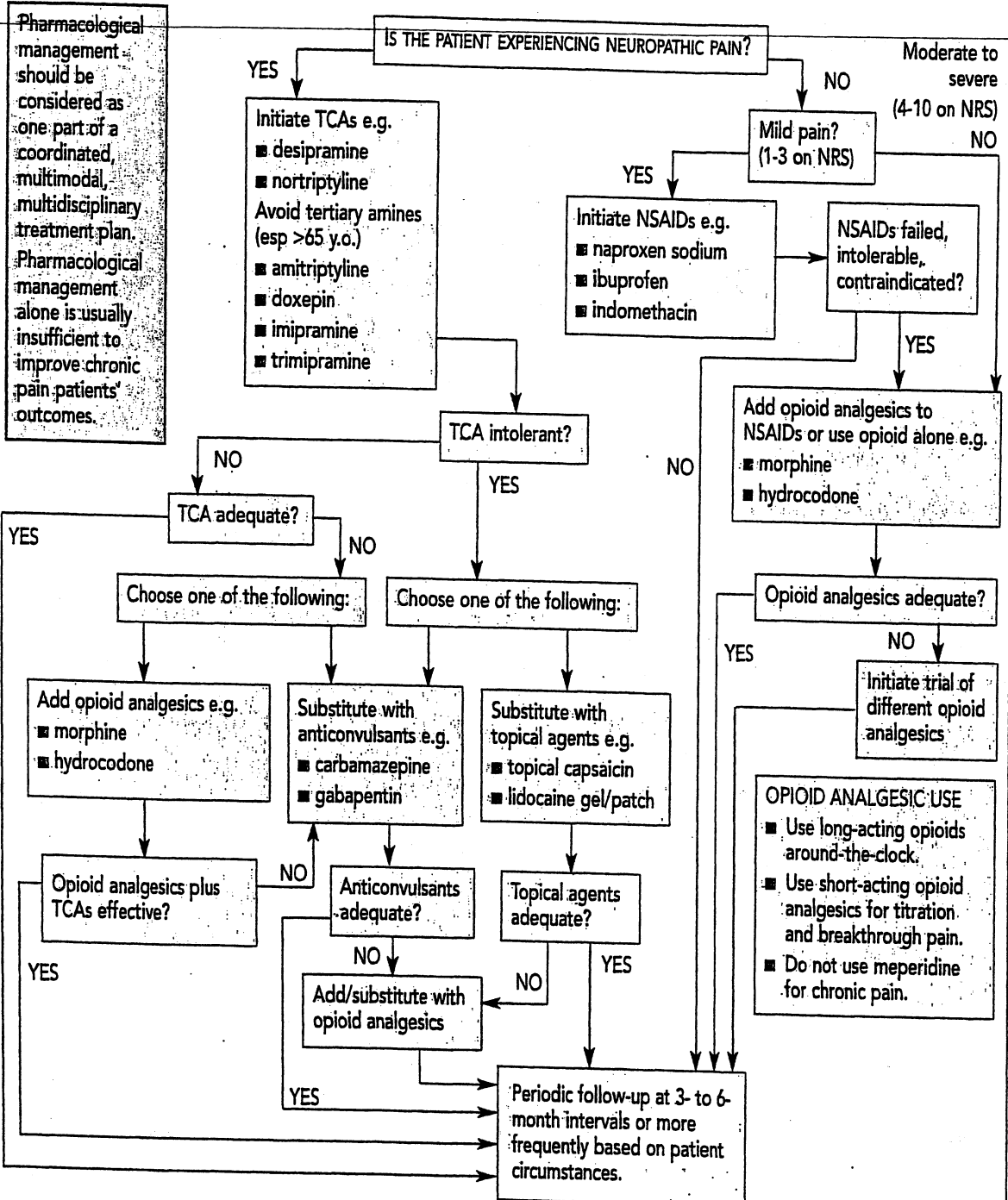
http://pkc.kp.org/national/cmi/programs/palliativecare/PC_CultComp.html#tools

NON-PHARMACOLOGICAL MANAGEMENT	
BENEFITS ARE SHOWN IN CURRENT EVIDENCE	BENEFITS ARE NOT YET CLEAR IN CURRENT EVIDENCE
<ul style="list-style-type: none"> ■ Cognitive Behavioral Therapy² ■ Physical Therapy for chronic pain ■ Exercise Therapy for chronic pain ■ Therapeutic Massage for chronic low back pain ■ Acupuncture for chronic low back and neck pain (short-term) and migraine and tension headache⁴ ■ Chondroitin⁵ for mild to moderate osteoarthritis of the knee or hip ■ Glucosamine⁵ for mild to moderate osteoarthritis 	<ul style="list-style-type: none"> ■ Manual Therapy ■ Mechanical & Self-Traction ■ Transcutaneous Electrical Nerve Stimulation (TENS)³ ■ Water Injections ■ Spinal Manipulation ■ Prolotherapy ■ S-Adenosyl L-Methionine (SAME)⁵ ■ Methylsulfonylmethane (MSM)⁵ ■ Devil's Claw (Harpagophytum procumbens)⁵ ■ EMG-Biofeedback for chronic low back and temporomandibular pain patients

Please refer to the CMI Chronic Pain Guidelines for further detail regarding these interventions.

- Some interventions are not uniformly covered throughout KP regions. Patients should contact member services for coverage information.
- Cognitive behavioral interventions should be introduced early as part of a multimodal approach to pain management. They generally should not be used as substitutes for analgesics. Cognitive Behavioral Therapy approaches should match the individuals beliefs and expectations. Approaches include:
 - Relaxation exercises, breathing, guided imagery, exercise and physical fitness, problem resolution, assertion training, activity pacing, and stress management
 - Goal-setting
 - Instruction on how to counter negative cognitions with more adaptive thoughts
- Clinicians who choose to use this modality should customize the application and parameter settings to each patient.
- Initiate trial of 4-6 acupuncture treatments. If effective, additional treatments may be given with periodic reassessment.
- Chondroitin, glucosamine, SAME, MSM, & Devil's Claw are not regulated by the US FDA and may have variable quality, content, and contaminants as is the case for any herb or supplement.

PHARMACOLOGICAL MANAGEMENT OF CHRONIC PAIN¹



¹If acute pain patient is at high risk for developing chronic pain, treat aggressively using similar algorithm.

Use antiarrhythmics only with referral to pain medicine specialist.

Invasive pain management interventions, e.g., therapeutic nerve blocks, are not addressed by these guidelines.

Please confer with your pain management specialist.

OPIOID ANALGESICS

DRUG	STARTING DOSE	EQUIANALGESIC DOSE IM/SC/IV	DOSE TOTAL	COST	COMMENT
HYDROCODONE HYDROCODONE/ACETAMINOPHEN			20-30 mg	\$	■ Limited to maximum
Vicodin® -5/500 mg Lortab® -5/500 mg	1-2 tablets q 4-6 hr				acetaminophen (4 g/day max or 2 g/day max in alcoholics or liver failure)
MORPHINE IMMEDIATE RELEASE TABLETS MSIR® -10, 15, 30 mg SUSTAINED RELEASE TABLETS Oramorph SR® -15, 30, 60, 100 mg MS Contin® -15, 30, 60, 100, 200 mg ORAL LIQUID MSIR Oral Solution® -2 mg/ml, 4 mg/ml MSIR Oral Concentrate® -20 mg/ml	7.5-15 mg q 3-4 hr 30 mg q 12 hr 30 mg q 12 hr 7.5-15 mg q 3-4 hr	10 mg	30 mg	\$ \$ \$\$\$ \$	■ Use immediate release morphine for titration until stable analgesia is reached and for breakthrough pain
OXYCODONE IMMEDIATE RELEASE TABLETS Oxy IR® -5 mg Roxicodone® -5 mg Oxycodone/Acetaminophen Percocet® -5/325, 7.5/500, 10/500 mg Roxicet® -5/325, 5/500 mg SUSTAINED RELEASE TABLETS Oxycontin® -10, 20, 40, 80 mg	5-10 mg q 3-4 hr 5 mg q 3-4 hr 1-2 tabs q 4-6 hr 20 mg q 12 hr		20 mg	\$ \$ \$\$\$\$	■ Limited to maximum acetaminophen (4 g/day max or 2 g/day max in alcoholics or liver failure)

* Approximate equianalgesic ratios: e.g., 10 mg of IV morphine = 30 mg PO morphine; 30 mg PO morphine = 20 mg oxycodone = 20-30 mg hydrocodone

** Cost Legend \$<\$25/month \$\$=\$25-50/month \$\$\$=\$50-100/month \$\$\$\$>\$100/month

Formulary status varies by region; check with your local Pharmacy Department.

Drugs listed in alphabetical order by generic name.

ADJUVANTS

DRUG	STARTING DOSE	COST	COMMENT
TRICYCLIC ANTIDEPRESSANTS (TCAs): desipramine (Norpramin®) nortriptyline (Aventyl®, Pamelor®)	<65 years: 25 mg qhs; increase dose 25 mg/day at 3-7 day intervals >65 years: 10 mg qhs; increase dose 10-mg/day at 3-7 day intervals as needed	\$	■ Tertiary amines (amitriptyline, doxepin, imipramine, and trimipramine) should not be used for older adults (>65 years old) with chronic pain ■ Some patients benefit from a dose range of 25-50 mg/day; often higher doses are necessary
ANTICONVULSANTS: carbamazepine (Tegretol®)	100 mg bid; titrate by 100-200 mg q 48 hr until analgesia or intolerance, up to 300 mg qid	\$	■ The usual effective range is 600-1200 mg /day, given every 6 to 8 hours ■ Monitor CBC at baseline, after several weeks, and every 3 to 4 months. Liver and renal function tested at baseline
gabapentin (Neurontin®)	300 mg qhs x 1 week, then 300 mg tid x 1 week, then titrate at weekly intervals up to 3600 mg/day until analgesia or intolerance, in following manner: 600 mg tid, 900 mg tid, 1200 mg tid	\$\$\$\$	■ The range for analgesic efficacy is 300- 3600 mg/day, given every 8 hours, though therapeutic benefits were noted at doses of 1800 mg/day or higher in two clinical trials

* Cost Legend \$<\$25/month \$\$=\$25-50/month \$\$\$=\$50-100/month \$\$\$\$>\$100/month

Formulary status varies by region; check with your local Pharmacy Department.

Drugs listed in order of preferred use.

Note: Most of these drugs are used off-label. There are some trials for their efficacy, but some have not been FDA approved for the use specified here.

SIDE EFFECTS MANAGEMENT

Anti-Emetic Medications

CAUSE OF VOMITING	DRUG	DOSE	COST
Initiation of opioid therapy	prochlorperazine (Compazine®)	10 mg PO tid or 25 mg PR bid	\$
Delayed gastric emptying	metoclopramide (Reglan®)	10-20 mg PO bid-qid or 10 mg/hr IV	\$
Vertigo	scopolamine (TransdermScop®)	Apply 1 transdermal patch every 3 days	Variable for IV
	meclizine (Antivert®)	12.5-50 mg PO tid	\$

* COST LEGEND \$<\$25/month \$\$=\$25-50/month \$\$\$=\$50-100/month \$\$\$\$>\$100/month

Manage Constipation Aggressively

CONSTIPATION	<ul style="list-style-type: none"> ■ Senokot®, 2-4 tabs q hs or bid + docusate, 100-240 mg qd or Pericolace® 1-2 tabs bid ■ If no BM in 2 days add bisacodyl or Dulcolax® suppository or sorbitol starting at 2-4 tbsp 2-3x a day until BM, especially when constipation is opioid related
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CONDITION	RED FLAGS	ACTION
CANCER	<ul style="list-style-type: none"> ■ History of cancer* ■ Unexplained weight loss ■ Age ≥50 ■ Failure to improve within 6 weeks with conservative treatment ■ Pain for more than 4-6 weeks ■ Rest pain ■ Severe nighttime pain 	<ul style="list-style-type: none"> ■ If malignant disease is suspected, imaging is indicated and CBC, ESR should be considered ■ Consider rectal exam. ■ Consultation based on findings
INFECTION	<ul style="list-style-type: none"> ■ Fever* ■ History of intravenous drug use ■ Recent bacterial infections or recent bacteremia, especially urinary tract, skin, or pneumonia ■ Immunocompromised states (steroid, organ transplants, diabetes, AIDS) ■ Rest pain ■ Recent invasive procedure 	<ul style="list-style-type: none"> ■ If infection in the spine is suspected, MRI, CBC, ESR, and/or UA are indicated ■ Consultation based on findings
CAUDA EQUINA SYNDROME	<p>USAB*</p> <ul style="list-style-type: none"> ■ Urinary retention or incontinence ■ Saddle anesthesia ■ Anal sphincter tone decrease/fecal incontinence ■ Bilateral lower extremity weakness/numbness or progressive neurological deficit <p>USAB may be accompanied by severe pain</p>	<ul style="list-style-type: none"> ■ Immediate surgical consultation ■ Immediate MRI of spine as appropriate
FRACTURE	<ul style="list-style-type: none"> ■ Use of corticosteroids* ■ Age ≥70 or history of osteoporosis ■ Recent significant trauma ■ Minor trauma or strenuous lifting (in older or potentially osteoporotic patients) ■ Potential pathologic fracture (see cancer work-up above) 	<ul style="list-style-type: none"> ■ L/S spine film may be indicated ■ If positive, consider consult to Physical Medicine or Orthopedics ■ Consider DEXA scan

*Indicates single most important red flag for each condition

Adapted from Kaiser Permanente Northern California, 2000 and Kaiser Permanente Southern California, 2000

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These guidelines are informational only. They are not intended or designed as a substitute for the reasonable exercise of independent clinical judgment by practitioners, considering each patient's needs on an individual basis. Guideline recommendations apply to populations of patients. Clinical judgment is necessary to design treatment plans for individual patients.

Acknowledgements

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To obtain additional copies of this guide, or copies of the CMI Chronic Pain Guidelines and/or Chronic Pain Management Program, please contact the CMI product line at 510-271-6426 or CMIproducts@kp.org.



KAISER PERMANENTE

GENERAL CHRONIC PAIN

***Definition:** "Chronic pain is defined as persistent or episodic pain of a duration or intensity that adversely affects the function or well-being of the patient, attributable to any nonmalignant etiology."

***Treatment Goals:**

1. Optimize pain control; realize that a pain-free state may not be achievable.
2. Minimize adverse outcomes and cost.
3. Enhance functional abilities and physical and psychological well-being.
4. Enhance the quality of life for patients with chronic pain.

*Adapted from Anesthesiology 1997;86:995-1004.

Management of Mild/ Moderate Pain

Drug		Dose	Comments
SIMPLE ANALGESIC			
Acetaminophen (OTC)		325-650mg Q4-6H	<ul style="list-style-type: none"> • Maximum 4000mg/day • Other analgesics and cold meds may contain additional APAP, adjust dose accordingly. • Contraindicated in hepatic disease.
NSAIDs			
Ibuprofen (Motrin) 200mg (OTC) 400mg, 600mg, 800mg (Rx)		400-800mg Q6-8H	<ul style="list-style-type: none"> • Preferred NSAID. • Maximum dose 3200mg/day. • Caution in patients with renal or hepatic dysfunction, peptic ulcer disease.
Naproxen (Naprosyn, Anaprox) Naproxen sodium 220mg (OTC) Naproxen 250mg, 375mg, 500mg (Rx)		250-500 BID	<ul style="list-style-type: none"> • Maximum 1250mg/day. • Caution in patients with renal or hepatic dysfunction, peptic ulcer disease.
Etorolac (Lodine) capsule: 200mg, 300mg tablet: 400mg		300-400mg BID-TID	<ul style="list-style-type: none"> • Lower GI Risk NSAID. • Caution in patients with renal or hepatic dysfunction, peptic ulcer disease.
Nabumetone (Relafen) 500mg tablet only		500mg 1-2 tabs BID	<ul style="list-style-type: none"> • Lower GI Risk NSAID. • Caution in patients with renal or hepatic dysfunction, peptic ulcer disease.
NARCOTICS			
CIII	Codeine/APAP APAP 300mg/codeine 15mg (Tylenol #2) APAP 300mg/codeine 30mg (Tylenol #3) APAP 300mg/codeine 60mg (Tylenol #4)	1-2 tabs Q4H	<ul style="list-style-type: none"> • APAP/Codeine 30mg = Tylenol #3 or TC3, most common dosage form. • Maximum 12 tabs/24hrs.



Management of Moderate/ Severe Pain

Short-acting Narcotic Agents

Drug		Dose	Comments
Narcotic Combinations			
CIII	Codeine/APAP	See above	
CIII	Hydrocodone/APAP (Vicodin) 5 mg / 500mg tablet only	1-2 tabs PO Q4-6H	<ul style="list-style-type: none"> Dose limited by APAP component Maximum dose: 4 grams/day (8 tabs per day), 2 grams in alcoholics (4 tabs/day)
CII	Oxycodone/APAP (Percocet) 5mg / 325 mg tablet only	1-2 tabs PO Q4-6H	<ul style="list-style-type: none"> Dose limited by APAP component Maximum: 4 grams/day (8 tabs per day), 2 grams in alcoholics (4 tabs/day)
CII	Oxycodone/ASA (Percodan) 5mg / 325 mg tablet only	1-2 tabs PO Q6H	<ul style="list-style-type: none"> ASA products should not be given to children
Individual Narcotic Agents			
CII	Morphine Sulfate Tablets: 15, 30mg Suppositories: 5, 10, 20, 30mg Oral solution (compounded) IV formulations available	10-30mg PO Q4H	<ul style="list-style-type: none"> No maximum dose with morphine Tolerance develops to most side effects except for constipation
CII	Oxycodone (Roxicodone) 5mg tablets	5mg PO Q6H	<ul style="list-style-type: none"> As potent or slightly more potent than morphine with similar addiction potential
CII	Hydromorphone (Dilaudid) Tablets: 2, 4mg Suppository: 3mg IV formulations available	2 - 4mg PO Q4-6H 3- 6mg PR Q4-6H	<ul style="list-style-type: none"> Use caution in patients with COPD or other preexisting respiratory depression. Contraindicated in patients with increased intracranial pressure.
CII	Meperidine Tablets: 50, 100mg IV formulations available	50-100mg PO Q3-4H	<ul style="list-style-type: none"> Seizure risk Should not be used in elderly or renal failure patients (accumulation of toxic metabolite) Contraindicated in patients on MAO inhibitors

Long Acting Narcotic Agents

Drug		Typical Dose	Comments
CII	Morphine Sustained Release (Oramorph) Tablets: 15, 30, 60, 100mg	BID	<ul style="list-style-type: none"> Oramorph is preferred sustained-release product and long acting agent on Formulary Swallow whole, do not crush or chew the tablets 24h stable dose with immediate release MS should be determined prior
CII	Methadone (Dolophine) Tablets: 5, 10, 40mg	5 - 20mg PO Q6-8H	<ul style="list-style-type: none"> Use for treatment of pain not restricted by DEA Can be difficult to titrate because serum half life is not linearly related with analgesic effect Maybe useful in patients with chronic pain unresponsive to other narcotics
CII	Fentanyl Patch (Duragesic®) Patches: 25, 50, 75, 100 mcg/hr	Apply patch Q72H	<ul style="list-style-type: none"> \$\$\$\$\$ Coverage with short acting agent needed when initiating patch due to delayed onset of action For patients with high requirements, multiple patches can be used.
CII	Oxycodone Sustained Release (Oxycontin) Tablets: 10, 20, 40, 80, 160mg	BID dosing	<ul style="list-style-type: none"> \$\$\$\$ NON-FORMULARY See handout

Oxycontin: Sustained Release Oxycodone

- Oxycontin is the fastest growing prescription narcotic in the US since its approval in 1995 reaching over \$1 billion dollars in sales in 2000. However, reports of significant problems of abuse and diversion across the country have prompted federal intervention. The DEA has initiated its first ever action program against a prescription drug, asking the manufacturer to limit its marketing and distribution to chronic pain specialists only. The highest strength formulation (160mg) has been voluntarily removed from the market. The FDA has recently required the manufacturer to strengthen its warnings on the product label, including the addition of a black box warning on the abuse potential associated with this product.
- In published clinical trials, Oxycontin has not been shown to more effective, better tolerated, or safer than sustained release morphine. However, the cost of Oxycontin at equi-analgesic doses is approximately 9-35x higher than Oramorph (preferred KP oral morphine sustained release product).

Oxycontin: Long-acting Alternatives with Equivalent Dosing

Drug	Dose
Oxycontin	10 mg PO Q12H
Morphine SR	15-30 mg PO Q12H
Fentanyl Patch	25 mcg/hr topical Q72H
Oxycontin	20 mg PO Q12H
Fentanyl Patch	50 mcg/hr topical Q72H
Oxycontin	30 mg PO Q12H
Morphine SR	60 mg PO Q12H
Fentanyl Patch	75 mcg/hr topical Q72H
Oxycontin	40 mg PO Q12H
Morphine SR	90 mg PO Q12H
Fentanyl Patch	100-125 mcg/hr topical Q72H
Oxycontin	60 mg (40 mg + 20 mg) PO Q12H
Morphine SR	120 mg PO Q12H
Methadone	5 mg PO Q6-8H
Fentanyl Patch	150-175 mcg/hr topical Q72H
Oxycontin	80 mg PO Q12H
Morphine SR	200 mg PO Q12H
Methadone	5mg PO Q6-8H
Fentanyl Patch	200-250 mcg/hr topical Q72H
Oxycontin	120 mg (80 mg + 40 mg) PO Q12H
Methadone	10 mg PO Q6-8H
Fentanyl Patch	300 mcg/hr topical Q72H

Partially adapted from Oxycontin Conversion Reference by Purdue Pharma

Starting or switching patients to sustained release morphine (Oramorph)

1. Start with low dose of immediate release morphine and titrate slowly to pain control. Tolerance to many of opioid-related side effects (nausea, vomiting, sedation) will develop over several days, except for constipation.
2. Once the patient is on a stable dose of morphine, calculate how much Oramorph the patient requires in a 24 hour period and give in 2 divided doses.
3. Titrate as needed to pain control. Sometimes this means titrating the dose downward to both maintain adequate pain control while reducing adverse effects.
4. Prevent constipation. Patients on routine doses of opioids become constipated and fiber laxatives are not very effective. Instruct the patient to take a stool softener plus a senna based laxative twice daily.
5. If switching from Oxycontin (or other narcotic) to Oramorph, a total 24 hour requirement should be calculated and converted to an equivalent dose of morphine. Give 50% of this dose to start (cross tolerance is incomplete) and titrate upward as needed. This will allow the patient the best chance to tolerate the new medicine

PAIN SYNDROMES

Diabetic Peripheral Neuropathy

- Tight glycemic control can relieve symptoms and slow progression of peripheral neuropathy.
- The first line treatment for diabetic peripheral neuropathy is tricyclic antidepressants (TCAs). Gabapentin may be an alternative for patients who have contraindications or do not tolerate TCAs.
- Although gabapentin use is escalating, its efficacy has only been shown to be superior to placebo. In a small, double blind, crossover comparison of gabapentin and amitriptyline for diabetic peripheral neuropathy, there was no significant difference in efficacy. Gabapentin had increased sedation and dizziness, while amitriptyline had an increase in dry mouth and weight gain.

Post-herpetic Neuralgia

- For small, localized areas initiate with topical lidocaine gel or cream. For larger areas or unresolved pain, initiate a TCA, such as nortriptyline. TCAs are well documented to improve post-herpetic neuralgia pain in 47-67% of patients.
- One study found gabapentin to be effective in 43% of patients. There are no studies comparing gabapentin to TCAs for post-herpetic neuralgia.

Number needed to treat to obtain 1 patient with >50% pain relief

Drug	Diabetic Neuropathy NNT	Post-herpetic Neuralgia NNT
TCA	2.4 patients	2.3 patients
Gabapentin	3.7 patients	3.2 patients

Data from Sindrup, S. et al Pain 1999;83:389-400.

Fibromyalgia

- The first line treatment for fibromyalgia is non-drug therapy (i.e. exercise). If medication is required, TCAs are the first-line drug treatment.
- For patients who do not respond or cannot tolerate TCAs, Selective Serotonin Reuptake Inhibitors (SSRIs) are a potential treatment.

Trigeminal Neuralgia

- Carbamazepine (Tegretol®) is considered the drug of choice for the treatment of trigeminal neuralgia with a 60-80% efficacy rate.

Choosing a TCAs

Amitriptyline is the most commonly used TCA for neuropathies. However, desipramine and nortriptyline are good alternatives to amitriptyline and cause less sedation and fewer anticholinergic effects. With all TCAs, the dose should be started low and titrated as needed and tolerated.

TCA dosing

The maintenance doses of TCAs for peripheral neuropathy are: amitriptyline 25-150 mg/day, desipramine 25-150 mg/day, and nortriptyline 10-75 mg/day. The TCA should be initiated at 10mg at bedtime and titrate by 10-25 mg every 7-10 days to effective dose. Dosage should be increased according to clinical response and any evidence of intolerance. Most patients will achieve pain control at relatively low doses (i.e. 50-100 mg qhs).

Drug	ACh	Sedation	Orthostatic hypotension
Desipramine (Norpramin)	+	+	+
Nortriptyline (Aventyl, Pamelor)	++	++	+
Amitriptyline (Elavil)	++++	++++	++
0-none; +slight; ++moderate; +++high; ++++very high; +++++highest			

Gabapentin

- The initial dose of gabapentin should be 300mg QHS. Increase by 300mg/day every 3 days until 600mg TID is reached.
- Side Effects (>10%): somnolence (19.3%), dizziness (17.1%), ataxia (12.5%), fatigue (11%).

Prepared September 2001 by Stacey Olvera, PharmD, and Doris Lew, PharmD, Pharmacy Operations/Drug Information Services, Oakland. Revised October 2002.

CONTRA COSTA HEALTH SERVICES
CONTRA COSTA REGIONAL MEDICAL CENTER
CONTRA COSTA HEALTH CENTERS

CHRONIC PAIN MEDICATION
AGREEMENT, PAGE 1

Chronic Pain Medication Agreement between (patient) _____
and (primary care provider) _____, MD/FNP.

In order to provide chronic narcotics safely and effectively:

- _____ Initial 1. The patient should keep regular appointments with his/her primary care provider at _____.
- _____ Initial 2. All prescriptions for "controlled medications" should be filled at only one pharmacy, which will be _____. This may be changed if the patient and provider agree. "Controlled medications" are drugs that are regulated by the Department of Justice or Drug Enforcement Agency. Examples are opioid pain medications such as morphine, methadone, hydrocodone (Vicodin), codeine, or _____.
- _____ Initial 3. All routine prescriptions for controlled medication should be written by the primary care provider. If he/she is not available, another physician will write a prescription. Medications will be refilled at regular visits and not after hours or on weekends.
- _____ Initial 4. If the patient requires Emergency Department care which includes opioid pain medicines, he/she will bring a copy of or describe this agreement to the doctor. The patient will be responsible for informing his/her primary care providers of any Emergency Department visits by the next working day. The patient consents to the release of the Emergency Department records and any other, past or future, medical records for review by his/her primary care provider.
- _____ Initial 5.a. The patient agrees to random, supervised urine tox screens and/or breathalyzer tests to be sure that nonprescribed mind or mood altering substances are not being used [including but not limited to opioids ("narcotics", e.g., heroin), cocaine and other stimulants, alcoholic beverages, benzodiazepines, (e.g., Valium) or other depressants and marijuana.]

A refusal to do a tox screen may be interpreted as the same as a positive test. A positive test, confirmed by our reference lab, may result in a gradual reduction of long-acting opioid analgesics or a clonidine-based detoxification. If this should occur, non-opioid pain treatment modalities will still be offered through Contra Costa Regional Medical Center and Health Centers.

CONTRA COSTA HEALTH SERVICES
CONTRA COSTA REGIONAL MEDICAL CENTER
CONTRA COSTA HEALTH CENTERS

CHRONIC PAIN MEDICATION
AGREEMENT, PAGE 2

OR

Initial

- 5.b. The patient agrees to follow his/her primary provider's advice and use alcoholic beverages in moderation, when doing so will not cause the patient medical or other problems.

The patient agrees to random, supervised urine tox screens and/or breathalyzer tests as requested by the examining provider to affirm that nonprescribed mind or mood altering substances are not being used [including, but not limited to, opioids ("narcotics", e.g., heroin), cocaine and other stimulants; benzodiazepines or other depressants, and marijuana.]

A refusal to do a tox screen may be interpreted as the same as a positive test. A positive test, confirmed by our reference lab, may result in a gradual reduction of long-acting opioid analgesics or a clonidine-based detoxification. If this should occur, non-opioid pain treatment modalities will still be offered through Contra Costa Regional Medical Center and Health Centers.

Initial

6. If the patient does **not** follow this agreement, the primary care provider may begin a gradual reduction of long-acting opioid medications or clonidine-based detoxification and continue it until the patient has a new primary care or pain management physician.

Initial

The patient has received information about the risks and benefits of chronic opioid medication and has had all of their questions answered satisfactorily.

This agreement should be reviewed and revised periodically, every 3 to 6 months, or as appropriate.

Patient

Date

Primary Care Provider

Date

Witness

CPM initiated by _____ on (date) _____

PATIENT INFORMATION ON CHRONIC OPIOID PAIN MEDICATIONS

1. Opioid pain medications such as morphine, oxycodone, hydrocodone, codeine, and others (also called "narcotics") are the strongest known pain relievers. Some patients report being able to do more when they take these medications and have less pain, but others do not. Most patients report good, but not complete pain relief.
2. It is important to understand that taking opioid medicines might interfere with a person's ability to concentrate and think clearly, and this side effect usually decreases in time. Side effects may also include constipation, dizziness, itching, nausea, and difficulty urinating.
3. Taking opioid pain medications for some time usually causes physical dependence. This means that if these medicines are stopped suddenly, a person might experience symptoms such as tearing, runny nose, difficulty sleeping, agitation, abdominal pain, nausea, vomiting, diarrhea, and severe discomfort.
4. Taking opioids ("narcotics") for some time might increase someone's risk of developing an addiction. This means that someone could become so focused on taking narcotics or other drugs that other important aspects of life, such as family, friends, work and health could suffer.
5. Individuals who have addictions are often unaware of their addictions. Thus, it is very important while taking opioid pain medicines that a doctor follow a patient closely to assess if they are developing an addiction.

Note to women: It is very important for non-pregnant women to use effective birth control to avoid becoming pregnant while taking chronic opioid pain medicines. If a woman wants to become pregnant or might be pregnant, it is very important to discuss this with the primary care provider immediately.

Pain Diary of _____

Bring this diary with you to your next appointment with Dr. _____

Record your pain characteristics every day.

Pain scale: 0=no pain, 1-3=mild, 4-6=moderate, 7-9=severe, 10=worst possible

DATE									
Where is your pain?									
RATE YOUR PAIN (1-10 scale)									
What were you doing before the pain started or increased?									
What medicines did you take? (name, dose)									
What other methods did you try? (relaxation, massage, heat, etc.)									
RATE YOUR PAIN 1 HOUR LATER (0-10 scale)									
OVER-ALL PAIN SCORE TODAY (0-10 scale)									
How well did you sleep last night?									
How weak do you feel?									
How dizzy/lightheaded do you feel?									
Are your bowel movements normal?									
How many times did you urinate today?									
What exercise did you do today? For how long?									
How is your thinking ability?									
How anxious do you feel?									
How depressed/frustrated are you?									
How angry/irritable are you?									
How happy are you?									

Use of opioids

Steven Stanos, DO

During the last decade, the importance of opioids in the management of chronic pain has evolved: opioids are now recommended as possible first-line therapies for many chronic pain disorders.^{1,2} As a result, several issues of opioid prescription confront primary care physicians: the distinction between tolerance, physical dependence, and addiction; achieving efficacy when an opioid no longer provides analgesia; and understanding the newer opioid options available for clinical use. Strategies for overcoming these common barriers to opioid use in a primary care practice are presented below.

Selecting Appropriate Patients for Opioid Therapy

Patients with chronic pain will certainly inform you of the degree of pain they are suffering. Nevertheless, a thorough diagnostic work-up and clinical assessment are necessary to determine if comorbid conditions may be contributing to the multidimensional experience of chronic pain. Major depression occurs in 30% to 60% of patients with chronic pain³ and 16% to 28% have adjustment disorder with anxious mood.⁴ Whether the pain is causing these comorbid conditions or vice-versa, it is important to evaluate and treat not only on biologic factors, but also the psychological and social issues.

A thorough pain history includes questions about non-pharmacologic interventions, prior effectiveness of medications, and an assessment of patient function and quality of life. Establishing empathy and a good rapport early in the management process will help establish realistic treatment goals for both the physician and the patient; such a relationship can also facilitate the assessment of risk for opioid abuse and poor compliance with treatment regimens. Patients should be asked about a personal or family history of alcohol or substance abuse; a brief screening instrument may also be useful.

Drug Abuse Assessment Tools

The CAGE questionnaire was originally developed to identify alcoholism.⁵ A modified version, called the CAGE-AID, is

LEARNING OBJECTIVES	
1. Apply a rational approach to selecting appropriate patients for long-term opioid therapy by balancing the risks and benefits.	
2. Explain the role of opioid analgesics in reducing pain and restoring patient function.	
3. Optimize the therapeutic response through opioid selection, titration, rotation, conversion, dose tapering, and use of adjunctive therapy.	
4. Assess and address patient outcomes in the domains of analgesia, activities of daily living, adverse effects, and aberrant drug-related behavior.	
5. Use practical tools and resources to aid documentation and compliance with controlled substance regulations.	
6. Identify effective clinical strategies for preventing abuse and diversion with opioids while effectively managing chronic pain.	

PRACTICE RECOMMENDATIONS	
Opioids have been established as an option for first-line therapy for many chronic pain disorders. (SOR: A)	
Assessing the risk for substance abuse is essential prior to initiating opioid therapy. (SOR: B)	
A tailored treatment approach should be implemented that might include informed consent, a medication agreement, and sustained-release and/or abuse-deterrent opioids. (SOR: C)	
The risk of legal and regulatory scrutiny can be minimized by using sound assessment and monitoring techniques, adhering to accepted principles of prescribing, keeping thorough documentation in the medical record, and knowing the federal and state regulations. (SOR: B)	

used to assess drug problems. CAGE is an acronym: the questionnaire asks if the patient has ever attempted to Cut down on drinking or drug use, been Annoyed with criticisms about drinking or drug use, felt Guilty about drinking or drug use,

FIGURE 1

Opioid Risk Tool		FEMALE	MALE
MARK EACH BOX THAT APPLIES:			
1. Family history of substance abuse			
Alcohol	<input type="checkbox"/> 1	<input type="checkbox"/> 3	
Illegal drugs	<input type="checkbox"/> 2	<input type="checkbox"/> 3	
Prescription drugs	<input type="checkbox"/> 4	<input type="checkbox"/> 4	
2. Personal history of substance abuse			
Alcohol	<input type="checkbox"/> 3	<input type="checkbox"/> 3	
Illegal drugs	<input type="checkbox"/> 4	<input type="checkbox"/> 4	
Prescription drugs	<input type="checkbox"/> 5	<input type="checkbox"/> 5	
3. Age (mark box if between 16 and 45 years)	<input type="checkbox"/> 1	<input type="checkbox"/> 1	
4. History of preadolescent sexual abuse	<input type="checkbox"/> 3	<input type="checkbox"/> 0	
5. Psychological disease			
ADD, OCD, bipolar disorder, schizophrenia	<input type="checkbox"/> 2	<input type="checkbox"/> 2	
Depression	<input type="checkbox"/> 1	<input type="checkbox"/> 1	
SCORING TOTALS:		<input type="text"/>	<input type="text"/>
ADMINISTRATION	SCORING		
• On initial visit	• 0-3: low risk (6%)		
• Prior to opioid therapy	• 4-7: moderate risk (28%)		
	• ≥8: high risk (>90%)		

ADD, attention deficit disorder; OCD, obsessive-compulsive disorder.
Webster LR, Webster RM. *Pain Med.* 2005;6:432-442.

FIGURE 2

Screener and Opioid Assessment for Patients With Pain (SOAPP)

Please answer these questions using the following scale:
0=Never 1=Seldom 2=Sometimes 3=Often 4=Very often

- How often do you have mood swings?
- How often do you smoke a cigarette within an hour after you wake up?
- How often have any of your family members, including parents and grandparents, had a problem with alcohol or drugs?
- How often have any of your close friends had a problem with alcohol or drugs?
- How often have others suggested that you have a drug or alcohol problem?
- How often have you attended an Alcoholics Anonymous or Narcotics Anonymous meeting?
- How often have you taken medication other than the way it was prescribed?
- How often have you been treated for an alcohol or drug problem?
- How often have your medications been lost or stolen?
- How often have others expressed concern over your use of medication?
- How often have you felt a craving for medication?
- How often have you been asked to give a urine screen for substance abuse?
- How often have you used illegal drugs (eg, marijuana, cocaine) in the past 5 years?
- How often, in your lifetime, have you had legal problems or been arrested?

Butler SF, et al. *Pain.* 2004;112:65-75.

and if she or he has ever used alcohol or drugs as an Eye opener to steady nerves or resolve a hangover. The test may be administered quickly and informally, thereby making it an effective screening tool for a family practice.

The CAGE questionnaire does not differentiate between current and former problems, and it is more accurate for detecting alcoholism than problem drinking. It is thought to be 60% to 90% sensitive when 2 or more questions are positive and 40% to 60% specific for excluding substance abuse.⁶ Just 1 positive response should raise concerns and 2 or more positive responses indicate a high likelihood of a serious alcohol or drug problem.

The validated Opioid Risk Tool (ORT) is easy to use in clinical practice (FIGURE 1).⁷ The ORT assesses risk factors associated with substance abuse: sex, personal and family history of substance abuse, age, history of preadolescent sexual abuse, and certain psychological diseases. Patient scores are grouped into 3 categories: low risk (0-3), moderate risk (4-7), or high risk (8 or more). The ORT is very sensitive and specific for determining a person's likelihood of displaying opioid-related aberrant behaviors.

The Screener and Opioid Assessment for Patients with Pain (SOAPP) is a self-administered, brief screening tool developed specifically to identify the risk of aberrant medication-related behaviors in patients under consideration for long-term opioid therapy.⁸ It is based on psychiatric and substance abuse history, doctor-patient relationship factors, and personal care and lifestyle issues. The SOAPP has demonstrated sensitivity and specificity over a 6-month period for patients with chronic pain. A score of 8 or higher on the 14-item screener identifies persons who are at high risk of aberrant opioid-related behavior (FIGURE 2).⁹

Differential Diagnosis of Aberrant Drug-Taking Attitudes and Behavior

Even with screening tools, it is not always possible to identify a person who will abuse opioids. Consequently, it is important to remain vigilant for aberrant drug-related behaviors after therapy begins. Passik et al noted behaviors that are more predictive of opioid abuse than others (TABLE 1)^{10,11}; used together with other information, these observations may be helpful.

The presence of aberrant behavior does not necessarily mean that opioid abuse is the cause, so investigation of the behavior is necessary. It is important to distinguish between tolerance, physical dependence, pseudoaddiction, and addiction. Because these terms are frequently misunderstood, the ways that each may be experienced in the office setting are described here.

Tolerance: Fortunately, tolerance to the adverse effects of opioid analgesics, such as somnolence and nausea, develops rapidly in most patients, allowing them to continue tak-

ing the opioid. Analgesic tolerance, however, occurs when progressively higher doses of opioids are required to maintain the same degree of pain control. It is important to distinguish analgesic tolerance from increasing analgesic requirements due to progression of the patient's pain condition. Retrospective case reports suggest that the development of analgesic tolerance in chronic pain patients is uncommon and is most relevant within the first 6 months of opioid use. Tolerance is one of the criteria for opioid addiction that is listed in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*.¹² According to a consensus document from the American Academy of Pain Medicine (AAPM), the American Pain Society (APS), and the American Society of Addiction Medicine (ASAM), however, tolerance "does not, in and of itself, imply addiction" and should not be used to diagnose addiction in the absence of other criteria.¹³

Physical dependence: Physical dependence is a common physiologic phenomenon associated with the regular use of opioids, as well as multiple other medication. It is characterized by the appearance of a constellation of signs and symptoms associated with the abrupt termination of regular opioid use. Common symptoms include tremors, sweats, chills, lacrimation, abdominal cramps, arthralgias and myalgias, vomiting, and diarrhea. Physical dependence, in the absence of other indicators, is neither predictive nor diagnostic of addiction. Most patients on scheduled opioid therapy become physically dependent. Although abrupt withdrawal of opioid therapy is not life-threatening, it is rarely necessary in the skilled and sensitive treatment of patients. If the need to discontinue long-term opioid therapy arises, gradual tapering of opioid therapy and the use of adjunctive medication are necessary to minimize withdrawal symptoms.

Pseudoaddiction: Pseudoaddiction describes patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications, may clock watch, and may appear to be displaying inappropriate drug-seeking behaviors. Pseudoaddiction can be distinguished from true addiction in that the behaviors resolve when the pain is effectively treated.¹⁴ Misunderstanding this phenomenon may lead the clinician to inappropriately stigmatize the patient with the label "addict" and incorrectly limit or withhold appropriate care. In the setting of unrelieved pain, the request for increases in medication dose requires careful assessment, renewed efforts to manage pain, and avoidance of stigmatizing labels.¹⁵

Addiction: In their consensus document, the AAPM, APS, and ASAM defined addiction in the context of pain treatment with opioids as "a persistent pattern of dysfunctional opioid use that may involve any or all of the following: adverse consequences associated with the use of opioids; loss of control

TABLE 1

Aberrant Drug-Taking Behaviors

Probably More Predictive	Probably Less Predictive
Selling prescription drugs	Aggressive complaining about need for higher doses
Prescription forgery	Drug hoarding during periods of reduced symptoms
Stealing or borrowing another patient's drugs	Requesting specific drugs
Injecting oral formulation	Acquisition of similar drugs from other medical sources
Obtaining prescription drugs from nonmedical sources	Unsanctioned dose escalation 1-2 times
Concurrent abuse of related illicit drugs	Unapproved use of the drug to treat another symptom
Multiple unsanctioned dose escalations	Reporting central nervous system effects not normally expected
Recurrent prescription losses	

Passik SD, et al. *Oncology (Williston Park)*. 1998;12:517-521, 524; Passik SD, et al. *Oncology (Williston Park)*. 1998;12:729-734.

over the use of opioids; and preoccupation with obtaining opioids, despite the presence of adequate analgesia."¹³

Older literature from chronic pain clinics reporting high rates of opioid abuse and addiction used nonstandardized diagnostic criteria.^{15,16} Although further controlled clinical trials in chronic pain are needed, overall the literature provides evidence that the development of iatrogenic addiction is rare when opioids are carefully prescribed for the relief of acute and cancer pain. Assessing the risk of addiction in each patient, therefore, is a fundamental element of safe, effective treatment.

Aberrant behaviors: Aberrant behavior describes dysfunctional activities a patient may display as a means of obtaining more of a specific type of drug. Forging prescriptions, obtaining prescriptions from more than 1 physician source, repeatedly increasing dosages, and stealing or selling drugs are all examples of aberrant behavior. Any evidence of aberrant behavior necessitates prompt investigational action by the clinician and treatment team.

Physicians should obviously be concerned about the potential for aberrant behavior, but they should not allow the potential for this development to preclude the appropriate use of opioids for patients in need. According to the AAPM, APS, and ASAM, "physicians who are practicing medicine in good faith and who use reasonable medical judgment regarding the prescription of opioids for the treatment of pain should not be held responsible for the willful and deceptive behavior of patients who successfully obtain opioids for non-medical purposes."¹⁷

When clarifying these differences with patients, clinicians should provide a patients a copy of the AAPM, APS, and ASAM consensus statement.¹³ In addition, patients can be referred to the peer-reviewed, patient education Web sites

Recently Approved Opioid Analgesics

The fentanyl buccal tablet was recently approved by the FDA for the management of breakthrough pain in patients with cancer who are tolerant to opioid therapy for their underlying persistent cancer pain.¹ Patients are considered to be opioid tolerant if they are taking at least 60 mg of oral morphine per day, at least 25 mcg of transdermal fentanyl per hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid for a week or longer.

Because life-threatening respiratory depression could occur at any dose in opioid nontolerant patients, the fentanyl buccal tablet is contraindicated in the management of acute or postoperative pain and is not indicated for use in nontolerant patients. Due to the higher bioavailability of fentanyl in the buccal tablet, it is not possible to substitute on a microgram-per-microgram basis when converting patients from other transdermal or oral delivery (ie, transmucosal) fentanyl products.

The efficacy of the fentanyl buccal tablet was demonstrated in a double-blind, placebo-controlled, crossover study in opioid-tolerant patients with cancer and breakthrough pain. Sixty-five percent of patients who entered the study achieved adequate analgesia with tolerable side effects during the 60-minute titration phase of the study; the median dose was 400 mcg.¹

Oxymorphone has been commercially available in the United States since 1959 in injectable and suppository dosage forms. It is more lipophilic than morphine and when administered intramuscularly, oxymorphone is several times more potent than morphine. Oxymorphone also has a faster onset of action than morphine.^{2,3}

The structure of oxymorphone is similar to hydromorphone, demonstrating both classic μ -receptor activity as well as δ -receptor affinity.⁴ The mechanism of action of oxymorphone is likely different than that of oxycodone, which in addition to μ -receptor binding, also demonstrates κ -receptor activity. Also unlike oxycodone, oxymorphone is not metabolized by the cytochrome P450 isoenzymes 2D6 and 3A4.⁵

In June 2006, the US Food and Drug Administration (FDA) approved oral immediate-release and extended-release tablet formulations of oxymorphone based on multiple clinical trials demonstrating efficacy and safety in various chronic pain and acute pain populations.

Oxymorphone extended release is indicated for the relief of moderate-to-severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.⁵ It has been shown in randomized controlled studies to provide analgesia comparable to oxycodone controlled release in ambulatory patients with moderate-to-severe chronic low back pain,² as well as to

morphine controlled release and oxycodone controlled release in adults with moderate-to-severe cancer pain³; all were administered every 12 hours. In both studies, oxymorphone extended release provided comparable pain relief and tolerability to the comparator opioids but at a lower dose. In the first placebo-controlled trial to demonstrate efficacy of an opioid in low back pain for 12 weeks, oxymorphone extended release provided efficacious, long-term analgesia at a stable dose and was generally well tolerated throughout the study period.⁴

Oxymorphone immediate release is indicated for the relief of moderate-to-severe acute pain when the use of an opioid is indicated.⁵ In patients with moderate-to-severe postsurgical pain, oxymorphone immediate-release, 10, 20, and 30 mg, every 4 to 6 hours provided significantly better pain relief for up to 48 hours than oxycodone immediate release 10 mg or placebo.⁷

As with all opioids, respiratory depression is an important potential risk of oxymorphone and, as a Schedule II controlled substance, the drug has an abuse liability similar to other opioid analgesics. To avoid potentially fatal overdose, the tablets are to be swallowed whole (not crushed or broken) and must not be consumed with alcohol.

References

1. Fentora [prescribing information]. Salt Lake City, Utah: Cephalon, Inc; 2006.
2. Hale ME, Dvergsten C, Gimbel J. Efficacy and safety of oxymorphone extended release in chronic low back pain: results of a randomized, double-blind, placebo- and active-controlled phase III study. *J Pain*. 2005;6:21-28.
3. Sloan P, Slatkin N, Ahdieh H. Effectiveness and safety of oral extended-release oxymorphone for the treatment of cancer pain: a pilot study. *Support Care Cancer*. 2005;13:57-65.
4. Prommer E. Oxymorphone: a review. *Support Care Cancer*. 2006;14:109-115.
5. Opana [prescribing information]. Chadds Ford, Pa: Endo Pharmaceuticals Inc; 2006.
6. Hale ME, Ahdieh H, Ma T, Rauck R. Efficacy and safety of OPANA ER (oxymorphone extended release) for relief of moderate to severe chronic low back pain in opioid-experienced patients: a 12-week, randomized, double-blind, placebo-controlled study. *J Pain*. 2006 Dec 1; Epub ahead of print.
7. Gimbel J, Ahdieh H. The efficacy and safety of oral immediate-release oxymorphone for postsurgical pain. *Anesth Analg*. 2004;99:1472-1477.
8. Passik SD, Kirsh KL. The need to identify predictors of aberrant drug-related behavior and addiction in patients being treated with opioids for pain. *Pain Med*. 2003;4:186-189.

TABLE

Recently Approved Opioid Analgesics^{1,4,5}

Opioid Analgesic	Half-Life (h)	Peak Effect (h)	Duration (h)	Comment
Oxymorphone, immediate release	7.3-9.4	NR	NR	
Oxymorphone, extended release	9.4-11.3	2	NR	Equianalgesic ratio of oxymorphone extended release to oxycodone controlled release is 1:2
Fentanyl, buccal tablet	2.6-11.7	35-45 min	NR	

NR, not reported.

Fentora [prescribing information]. Salt Lake City, Utah: Cephalon, Inc; 2006; Prommer E. *Support Care Cancer*. 2006;14:109-115; Passik SD, Kirsh KL. *Pain Med*. 2003;4:186-189.

TABLE 2

Pure mu-Agonists Used for Pain Management in the United States

Opioid Analgesic	Equianalgesic doses** (mg)	Half-Life (h)	Peak Effect (h)	Duration (h)	Comments
Morphine	10 IM/IV/SQ 20-30 PO*	2-3 2-3	0.5-1 1-2	3-4 3-6	Standard for comparison of opioids; multiple routes of administration available
Morphine, controlled release	20-30 PO*	2-3	NA	8-12	
Morphine, sustained release	20-30 PO*	2-3	NA	12-24	Once-a-day morphine
Hydromorphone	1.5 IM/IV/SQ 7.5 PO	2-3 2-3	0.5-1 1-2	3-4 3-6	Potency and high solubility may be beneficial for patients requiring high opioid doses and for SQ administration
Oxycodone	20-30 PO	2-3	1-2	3-6	Available as single entity or combined with aspirin or acetaminophen
Oxycodone, controlled release	20-30 PO	NA	3-4	8-12	
Oxymorphone	1 IM/IV/SQ 10 PR	NA NA	0.5-1 1-3	3-6 4-6	
Levorphanol	2 IM/IV/SQ 4 PO	12-15 12-15	0.5-1 1-2	3-6 3-6	With long elimination half-life, accumulation possible after beginning or increasing dose
Methadone	Variable	12-150	1-2	6-8	Highly variable elimination half-life and potential for accumulation require increased vigilance for development of opioid toxicity; can prolong QTc interval
Hydrocodone	30 PO	2-4	1-2	3-6	Available only in combination with acetaminophen or aspirin
Fentanyl	50-100 mcg IV/SQ	7-12	<10 min	1-2	Can be administered as continuous IV or SQ infusion
Fentanyl, transdermal system	NA	NA	12-24	48-72 per patch	Refer to package insert for equianalgesic dosing guidelines for oral and parenteral medication; currently available doses not usually recommended for opioid-naïve patients; not recommended for acute pain
Fentanyl citrate, oral transmucosal	NA	7-12	15-30 min	1-2	Not recommended for opioid-naïve patients; recommended starting dose for breakthrough pain is 200-400 mcg, even with high "baseline" opioid

IM, intramuscular; IV, intravenous; NA, not applicable; PO, by mouth; PR, per rectum; SQ, subcutaneous.

* Dose provides analgesia equivalent to 10 mg of morphine given by the IM route. These ratios are useful guides when switching drugs or routes of administration. In clinical practice, the potency of the IM route is considered to be identical to IV and SQ routes.

† When switching from one opioid to another, incomplete cross-tolerance requires a reduction in the dose of the new drug by 25% to 50% to prevent excessive opioid effects. Provision of "rescue" medication during the conversion period (a few days) prevents breakthrough pain that might result from relative underdosing. When switching to methadone from another drug, the reduction in the equianalgesic dose should be greater, usually 75% to 90%.

‡ Extensive survey data suggest that the relative potency ratio of IM to PO morphine, which has been shown to be 1:6 in an acute dosing study, is 1:2 to 1:3 with chronic dosing. Fine PG, Portenoy RK. New York, NY: McGraw Hill; 2004.

of the American Pain Foundation (www.painfoundation.org) or the National Pain Foundation (www.nationalpainfoundation.org).

Role of Opioid Therapy

Numerous randomized clinical trials and systematic reviews of randomized controlled trials support the role of opioids as first-line therapy for moderate-to-severe pain.¹⁸⁻²⁰ (See

Adjuvant Analgesics for the Treatment of Neuropathic Pain on page 3 for a discussion of opioids in neuropathic pain.) Most opioid analgesic classes have been commercially available for a decade or more and are well known to primary care clinicians (TABLE 2).²¹ The agents classically bind to mu (μ), delta (δ), and kappa (κ) receptors. Two new analgesic compounds, the fentanyl buccal tablet and oral oxycodone, became available for clinical use in 2006 (PAGE 26).

TABLE 3

Federation of State Medical Boards Criteria For Evaluating the Physician's Treatment of Pain

<p>Evaluation of the Patient</p> <p>Obtain a medical history and conduct a physical examination; document these steps in the medical record.</p> <p>The medical record should document:</p> <ul style="list-style-type: none"> • Nature and intensity of the pain • Current and past treatments for pain • Underlying or coexisting diseases or conditions • Effect of the pain on physical and psychological function • History of substance abuse • Presence of one or more recognized medical indications for the use of a controlled substance 	<ul style="list-style-type: none"> • Satisfactory response, indicated by the patient's decreased pain, increased level of function, or improved quality of life • Objective evidence of improved or diminished function, based on information from family members or other caregivers who are monitoring treatment <p>Assess the appropriateness of continuing the current treatment plan if the patient's progress is unsatisfactory and consider the use of other therapeutic modalities.</p>
<p>Treatment Plan</p> <p>The written treatment plan should:</p> <ul style="list-style-type: none"> • State objectives that will be used to determine treatment success, such as pain relief and improved physical and psychosocial function • Indicate if any further diagnostic evaluations or other treatments are planned <p>Adjust plan as needed to the individual medical needs of each patient.</p> <p>Include other treatment modalities or a rehabilitation program in treatment plan, depending on the etiology of the pain and the extent to which the pain is associated with physical and psychosocial impairment.</p>	<p>Consultation</p> <p>Refer as necessary for additional evaluation and treatment in order to achieve treatment objectives.</p> <p>Pay special attention to patients at risk for medication misuse, abuse, or diversion.</p> <p>Provide extra care, monitoring, documentation, and consultation with or referral to pain specialist when treating patients with a history of substance abuse or with a comorbid psychiatric disorder.</p>
<p>Informed Consent and Agreement for Treatment</p> <p>Discuss the risks and benefits of the use of controlled substances with the patient/designee/surrogate/guardian.</p> <p>Obtain the patient's agreement to receive prescriptions from 1 physician and 1 pharmacy whenever possible.</p> <p>Develop a written agreement with a patient at high risk for medication abuse or with a history of substance abuse, that includes:</p> <ul style="list-style-type: none"> • Urine/serum medication levels screening • Number and frequency of all prescription refills • Reasons for which drug therapy may be discontinued (eg, violation of agreement) 	<p>Medical Records</p> <p>Keep accurate and complete records that include:</p> <ul style="list-style-type: none"> • Medical history and physical examination • Diagnostic, therapeutic, and laboratory results • Evaluations and consultations • Treatment objectives • Discussion of risks and benefits • Informed consent • Treatments • Medications (including date, type, dosage, and quantity prescribed) • Instructions and agreements • Periodic reviews <p>Keep records current and maintain them in an accessible manner so that they are readily available for review.</p>
<p>Periodic Review</p> <p>Follow up regarding the course of pain treatment and any new information about the etiology of the pain or the patient's state of health.</p> <p>Determine whether to continue or modify use of controlled substances for pain management therapy, depending on progress toward treatment objectives according to the following factors:</p>	<p>Compliance With Controlled Substances Laws and Regulations</p> <p>Note that to prescribe, dispense, or administer controlled substances, the physician must be licensed in the state and comply with applicable federal and state regulations.</p> <p>Refer to the Physicians' Manual of the US Drug Enforcement Administration and (any relevant documents issued by the state medical board) for specific rules governing controlled substances as well as applicable state regulations.</p>

Federation of State Medical Boards of the United States, Inc. Available at: www.fsmb.org/pdf/2004_grpol_Controlled_Substances.pdf. Accessed January 2, 2007.

Initial Steps to Prescribing an Opioid: Obtain Informed Consent

Informed consent and medication agreements are necessary under many circumstances when opioids are to be prescribed. In addition to clarifying the rules under which opioid therapy will be provided, these steps provide opportunities for patient education.

Informed consent should be obtained for all patients who are to be treated long-term with opioid analgesics. Informed consent for short-term use of opioids is advised for those who have been assessed as being at increased risk for abuse. These

documents should describe the benefits and risks of the opioid, as well as the goals of therapy. Other issues to include are the importance of regular visits and compliance with the opioid treatment plan, the consequences of recreational drug use, and the number of physicians and pharmacies to be used for opioid prescriptions. A consent form may be obtained from the AAPM (www.painmed.org/productpub/statements/pdfs/opioid_consent_form.pdf).

In addition to informed consent, a medication agreement is advised prior to initiating opioid therapy in patients at increased risk for substance abuse. Previously called an opioid

contract, a medication agreement outlines the treatment plan, establishes the responsibilities of the patient and physician, and explains the rules under which opioid therapy will be provided. The medication agreement identifies the actions that will be taken should the patient not comply with the terms of the medication agreement. It is, of course, important that the physician also comply with her/his responsibilities as stated in the agreement.²² A sample medication agreement is available from the AAPM (www.painmed.org/productpub/statements/pdfs/controlled_substances_sample_agmt.pdf).

A trilateral medication agreement can be used in situations in which opioid therapy is prescribed by a provider other than the primary care physician. An important benefit of the trilateral medication agreement is that it can serve to promote good communication among the primary care physician, pain specialist, and patient.²³

Establishing a Patient-Specific Chronic Pain Management Program

Dividing patients with chronic pain into 3 groups stratified by the risk of developing aberrant behavior can be useful to tailor the treatment plan. One group consists of uncomplicated patients: approximately 55% of patients do not exhibit any aberrant behavior.

At the other end of the spectrum are individuals with either active abuse disorders or a history of substance abuse, or patients whose risk of opioid abuse is unclear at the time opioid therapy is initiated. Once a history is established for the latter patients, they should be reassessed and possibly recategorized.

The middle group includes patients who have poor coping skills and lack motivation; many time people in this group are unmotivated for active treatment. These "chemical copers" comprise approximately 25% of patients, who will often take their medications indiscriminately and frequently suffer from comorbid psychiatric disorders.^{24,25}

Uncomplicated patients may be managed with routine medical care. These persons can be given a regular 30-day supply of opioid(s) and other pain medications, as well as permission for the use of more liberal rescue medication for breakthrough pain. However, frequent use of rescue opioids should prompt a reassessment of the treatment plan. A brief monthly follow-up is often adequate.

For the middle group, the treatment plan should not be as liberal as with the uncomplicated patient. Drug regimens should be simple and implemented in such a way to dissuade the indiscriminate use of medications. In addition, rehabilitation, psychiatric interventions, and management of contributing comorbidities should be the primary focus of management. The presence of aberrant behaviors should be assessed regularly.

For a patient at increased risk of opioid abuse, it is appropriate to reexamine the need for an opioid. Factors to

TABLE 4

The Four "A"s of Pain Treatment Outcomes

- Analgesia (pain relief)
- Activities of daily living (psychosocial functioning/quality of life)
- Adverse effects (side effects)
- Aberrant drug-taking behavior (addiction-related outcomes)

Passik SD, Weinreb HJ. *Adv Ther*. 2000;17:70-83.

TABLE 5

The 10 Steps of Universal Precaution in Pain Medicine

1. Make a diagnosis with appropriate differential
2. Psychological assessment, including risk of addictive disorders
3. Informed consent
4. Treatment agreement
5. Pre- or postintervention assessment of pain level and function
6. Appropriate trial of opioid therapy with or without adjunctive medication
7. Reassessment of pain score and level of function
8. Regularly assess the "4 A's" of pain medicine
9. Periodically review pain diagnosis and comorbid conditions, including addictive disorders
10. Documentation

Gourlay D, et al. *Pain Med*. 2005;6:107-112.

consider include the pain diagnosis, the effect of pain on the patient's activities of daily living and quality of life, medical comorbidities, nonpharmacologic and pharmacologic treatments previously used and the reasons for failure (lack of benefit vs side effects), use of therapies to prevent or manage side effects, and evidence of previous pain treatment adherence and/or compliance.

If the need for and appropriateness of an opioid is verified and the patient's commitment to the agreed-upon treatment plan is confirmed, cautious use of a maximally structured approach is recommended; informed consent and a medication agreement should certainly be included. Many strategies promote and verify the patient's adherence with therapy, such as pill counts, urine toxicology screens, and unscheduled office visits with short notification. If possible, an opioid that is not being abused in the local region should be used. Referral to or consultation with a pain specialist may be helpful.

Practical Patient-Monitoring Tools

The Federation of State Medical Boards (FSMB) outlines 7 steps clinicians should follow when prescribing controlled substances for the treatment of pain (TABLE 3).²⁶ A common theme of these 7 steps is accurate and adequate documentation regarding the care of a patient with pain.

Another approach, not outlined in the FSMB Model Policy, follows the 4 outcome domains of importance when treating a patient with chronic pain (TABLE 4). These have become known as the 4 "A"s, ie, analgesia, activities of daily living, adverse effects, and aberrant drug-taking behavior.²⁷ At each patient evaluation, the medical record should indicate that each of the 4 "A"s has been assessed and the presence or absence of specific signs, symptoms, or behaviors noted. When a change in therapy is warranted, the rationale based on the assessment should be documented.

Optimizing Therapeutic Response Dosing and Titration Principles

As a result of each opioid's distinct pharmacokinetic, pharmacodynamic, and side effect profile, treatment response is highly variable among patients. Generally, elderly patients require a lower opioid dose to achieve effective pain relief than younger patients do and neuropathic pain usually requires higher opioid doses than nociceptive pain.

The dosing principle used in all types of pain management with opioids is known as "dosing to effect." Opioid analgesics should be started at a low dose and carefully titrated until an adequate level of analgesia is obtained, or until persistent and unacceptable side effects warrant a reevaluation of therapy. It is generally believed that a ceiling dose does not exist for pure μ -agonist opioids; therefore, increasing the dose may produce additional analgesia. In a number of selected trials, titration to modest doses (up to 120 mg of morphine equivalents per day) not only provided pain relief, but improved sleep and functional status without impairing cognitive function.²⁸⁻³⁰

Breakthrough Pain

Some patients already receiving high doses of opioid agents may still experience periods of breakthrough pain. In fact, it has been estimated that 19% to 95% of patients with chronic pain will experience some degree of breakthrough pain, depending on the definition used.²⁶ Breakthrough pain is classified as incident, idiopathic, or end-of-dose failure.²⁶

Incident pain occurs when a normal movement such as walking creates a degree of pain that breaks through the analgesia level of the patient. Incident pain is the most common category of breakthrough pain, representing approximately 50% of the breakthrough pain episodes.

When no cause of the breakthrough pain can be identified, it is classified as idiopathic.

End-of-dose failure occurs when a patient's around-the-clock opioid dose is insufficient. The patient's pain will escalate or spike at the end of a dosing interval. Typically, this kind of pain is gradual in onset and has a longer duration than both incident pain that is related to movement and idiopathic forms of breakthrough pain.

Opioid Rotation

Opioid rotation is a therapeutic option for patients who do not achieve acceptable analgesia despite escalating doses or as a result of dose-limiting opioid side effects. Opioid rotation involves discontinuing 1 opioid and replacing it with a second opioid.

The dose of the second opioid must be carefully selected due to incomplete cross-tolerance. Incomplete cross-tolerance means that patients may have developed tolerance to the analgesia and side effects of the opioid they are currently taking. When they are switched to another opioid, tolerance may not be present to the same degree. Therefore, the new opioid is more potent and likely has more side effects. Consequently, switching or rotating agents requires initiating treatment with the second opioid at a daily dose 30% to 50% lower than the equianalgesic dose of the first. If necessary, the dose of the second opioid may be slowly increased until adequate analgesia is achieved.^{31,32}

Although methadone has become an attractive option for opioid rotation, it has a long and variable elimination half-life, possibly leading to drug accumulation. It is also difficult to establish equianalgesic doses of methadone and other opioids. These factors make its use in the primary care setting unadvisable.³³ Recent increases in the number of reports of fatal respiratory depression associated with methadone therapy underscore the potential risks associated with methadone conversion unless performed by someone knowledgeable and skilled in this regard.

The rationale for opioid rotation includes interpatient variability of response, incomplete cross-tolerance, and the interaction between specific opioids, particularly in terms of hepatic metabolism via the cytochrome P-450 system. For example, morphine, codeine, hydrocodone, oxycodone, and methadone are metabolized via the CYP2D6 hepatic enzyme. If a person is a slow metabolizer at the CYP2D6 hepatic enzyme, or is taking concomitant medications that also are metabolized through this same pathway (eg, a tricyclic antidepressant or selective serotonin reuptake inhibitor), an opioid that is not metabolized through the CYP2D6 hepatic enzyme (eg, fentanyl, oxymorphone) may be a rational choice when considering opioid rotation.

Overcoming Barriers

Despite the documented effectiveness of opioids in chronic pain management,^{17,34-36} many physicians still limit their prescribing of opioids due to concerns about ceiling analgesia, side effects, and long-term use.³⁷⁻³⁹

It is a misperception that opioids have a ceiling analgesia effect or that tolerance commonly develops after long-term use. Actually, it is because the analgesic effect of the pure opioids does not reach a ceiling that doses can be titrated to meet the patient's needs.⁴⁰ In addition to subjective

reports of pain, ongoing assessment of opioid response should also include specific measures or inquiries related to changes in function.

The expectation that the side effects of opioids will affect quality of life and medication adherence may inhibit opioid prescription. In fact, many opioid side effects resolve and others can be prevented or treated. Constipation, for example, typically does not resolve, and requires preventive treatment. However, cognitive and psychomotor impairment usually resolve once a person has adapted to a specific dose of an opioid.⁴¹⁻⁴⁸ Persons in highly skilled jobs have been shown to function well while taking opioids, while noting that untreated pain has more of a deleterious effect on their concentration and performance than do opioids.^{40,48}

Older persons may be at greater risk for cognitive and psychomotor effects, but these effects appear to be limited to the acute use of opioids.⁴⁰⁻⁴⁸ Concomitant administration of opioids with other central nervous system depressants must be done cautiously, if at all, due to the additive effects. Examples of such depressants include alcohol (including alcohol in some oral liquid formulations such as cough syrup), sedative/hypnotics, some antidepressants, phenothiazines, and sedating antihistamines.

From research on addiction, it appears that long-term use of opioids can be associated with the development of abnormal pain sensitivity and may contribute to the development of opioid tolerance. Hormonal changes are also evident through effects on the hypothalamic-pituitary-adrenal axis and the hypothalamic-pituitary-gonadal axis, increasing prolactin and decreasing luteinizing hormone, follicle-stimulating hormone, testosterone, and estrogen. Opioids may affect immunity directly or through their neuroendocrine effects. As a consequence, the development, differentiation, and function of immune cells are affected, as are the innate and adaptive systems.⁴⁹ Therefore, follow-up assessments should also focus on monitoring of change in sexual function, libido, increased lethargy, sleep disturbance, and depression.

Universal Precaution

The initial approach to patients with an unknown infectious status is universal precaution to reduce the chance of an infectious transmission. This same concept has recently been applied to the initial assessment of chronic pain patients.⁵⁰ The 10 principles listed in **TABLE 5** will aid the primary care physician in identifying and interpreting potential aberrant behaviors. For patients at risk for addictive disorders, treatment plans can be adjusted on a patient-by-patient basis. Adopting a universal precautions approach to the chronic pain patient will be an important step in raising the standard of care in this often-complex patient population.

Regular Follow-Up

As with long-term therapy for any condition, regular follow-up and reassessment are critical to achieving the treatment goals. Although many patients with chronic pain will experience acceptable and stable pain relief for long periods of time, those who do not must have their treatment plan modified. Failure to change the treatment plan despite poor response or failure not only indicates substandard patient care, but also suggests an unwillingness of the clinician to assess for possible opioid abuse or diversion.

When a problem with an opioid is suspected, it must be appropriately investigated. Means of doing so include pill counts, patient questioning, behavior assessment/screening, urine drug testing, and random office visits with short notice given via telephone. Appropriate action, as described in the medication agreement, should be taken if a problem with the opioid is identified.

Thorough documentation in the medical record is vital. Clinicians should remain up to date regarding local, regional, state, and federal prescribing and treatment guidelines.

Discontinuing Opioid Therapy

Given the challenging nature of chronic pain management and the added issues with opioid therapy, discontinuation of opioid therapy may be considered under some circumstances, including inadequate pain relief, intolerable side effects, or opioid misuse or abuse. Because patients who have taken opioids on a regular basis are physically dependent, a tapering schedule should be used to avoid withdrawal. Alternative analgesia should be initiated as appropriate to avoid a compensatory increase of pain. Documentation in the medical record should include the reasons for discontinuing opioid therapy, the new or adjusted treatment plan, and communication with the patient that reflects her or his understanding.

Summary

Opioids are potent analgesics that are a first-line option for many types of chronic pain. Numerous barriers to the use of opioids exist, including inadequate education and training on how to use opioids appropriately, concern about side effects, regulatory requirements, and the potential for misuse, abuse, and diversion. Careful patient selection and a tailored treatment approach based on the assessment of risk can provide adequate analgesia with tolerable side effects, while deterring misuse and abuse. Regular monitoring helps to ensure that treatment goals are achieved and aberrant drug behaviors are avoided. Thorough documentation in the medical record at all stages of management is essential. ■

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